# PROTEASOME INHIBITORS

## RELATED APPLICATIONS

**[0001]** This application is a continuation of U.S. patent application Ser. No. 14/492,446, filed Sep. 22, 2014, which is a continuation of U.S. patent application Ser. No. 13/964,708, filed Aug. 12, 2013, now U.S. Pat. No. 8,871,745, which is a continuation of U.S. patent application Ser. No. 13/209,511, filed Aug. 15, 2011, now U.S. Pat. No. 8,530,694, which is a continuation of U.S. patent application Ser. No. 12/704,830, filed on Feb. 12, 2010, now U.S. Pat. No. 8,003,819, which is a continuation of U.S. patent application Ser. No. 12/217,243, filed on Jul. 2, 2008, now U.S. Pat. No. 7,687,662, which is a continuation of U.S. patent application Ser. No. 11/890,412, filed on Aug. 6, 2007, now U.S. Pat. No. 7,442,830 B1, of which each application is hereby incorporated by reference in its entirety.

## FIELD OF THE INVENTION

**[0002]** The present invention relates to boronic acid and boronic ester compounds useful as proteasome inhibitors. The invention also provides pharmaceutical compositions comprising the compounds of the invention and methods of using the compositions in the treatment of various diseases.

## BACKGROUND OF THE INVENTION

**[0003]** Boronic acid and ester compounds display a variety of pharmaceutically useful biological activities. Shenvi et al., U.S. Pat. No. 4,499,082 (1985), discloses that peptide boronic acids are inhibitors of certain proteolytic enzymes. Kettner and Shenvi, U.S. Pat. No. 5,187,157 (1993), U.S. Pat. No. 5,242,904 (1993), and U.S. Pat. No. 5,250,720 (1993), describe a class of peptide boronic acids that inhibit trypsin-like proteases. Kleeman et al., U.S. Pat. No. 5,169,841 (1992), discloses N-terminally modified peptide boronic acids that inhibit the action of renin. Kinder et al., U.S. Pat. No. 5,106,948 (1992), discloses that certain boronic acid compounds inhibit the growth of cancer cells. Bachovchin et al., WO 07/0005991, discloses peptide boronic acid compounds that inhibit fibroblast activating protein.

**[0004]** Boronic acid and ester compounds hold particular promise as inhibitors of the proteasome, a multicatalytic protease responsible for the majority of intracellular protein turnover. Adams et al., U.S. Pat. No. 5,780,454 (1998), describes peptide boronic ester and acid compounds useful as proteasome inhibitors. The reference also describes the use of boronic ester and acid compounds to reduce the rate of muscle protein degradation, to reduce the activity of NF-κB in a cell, to reduce the rate of degradation of p53 protein in a cell, to inhibit cyclin degradation in a cell, to inhibit the growth of a cancer cell, and to inhibit NF-κB dependent cell adhesion. Furet et al., WO 02/096933, Chatterjee et al., WO 05/016859, and Bernadini et al, WO 05/021558 and WO 06/08660, disclose additional boronic ester and acid compounds that are reported to have proteasome inhibitory activity.

**[0005]** Ciechanover, Cell, 79: 13-21 (1994), discloses that the proteasome is the proteolytic component of the ubiquitin-proteasome pathway, in which proteins are targeted for degradation by conjugation to multiple molecules of ubiquitin. Ciechanover also discloses that the ubiquitin-proteasome pathway plays a key role in a variety of important physiological processes. Rivett et al., *Biochem. J.* 291:1 (1993) discloses that the proteasome displays tryptic-, chymotryptic-, and peptidylglutamyl peptidase activities. Constituting the catalytic core of the 26S proteasome is the 20S proteasome. McCormack et al., *Biochemistry* 37:7792 (1998), teaches that a variety of peptide substrates, including Suc-Leu-Leu-Val-Tyr-AMC, Z-Leu-Leu-Arg-AMC, and Z-Leu-Leu-Glu-2NA, wherein Suc is N-succinyl, AMC is 7-amino-4-methylcoumarin, and 2NA is 2-naphthylamine, are cleaved by the 20S proteasome.

**[0006]** Proteasome inhibition represents an important new strategy in cancer treatment. King et al., *Science* 274:1652-1659 (1996), describes an essential role for the ubiquitin-proteasome pathway in regulating cell cycle, neoplastic growth and metastasis. The authors teach that a number of key regulatory proteins, including, cyclins, and the cyclin-dependent kinases p21 and $p27^{KIP1}$, are temporally degraded during the cell cycle by the ubiquitin-proteasome pathway. The ordered degradation of these proteins is required for the cell to progress through the cell cycle and to undergo mitosis.

**[0007]** Furthermore, the ubiquitin-proteasome pathway is required for transcriptional regulation. Palombella et al., *Cell,* 78:773 (1994), teaches that the activation of the transcription factor NF-κB is regulated by proteasome-mediated degradation of the inhibitor protein IκB. In turn, NF-κB plays a central role in the regulation of genes involved in the immune and inflammatory responses. Read et al., *Immunity* 2:493-506 (1995), teaches that the ubiquitin-proteasome pathway is required for expression of cell adhesion molecules, such as E-selectin, ICAM-1, and VCAM-1. Zetter, *Seminars in Cancer Biology* 4:219-229 (1993), teaches that cell adhesion molecules are involved in tumor metastasis and angiogenesis in vivo, by directing the adhesion and extravastation of tumor cells to and from the vasculature to distant tissue sites within the body. Moreover, Beg and Baltimore, *Science* 274:782 (1996), teaches that NF-κB is an anti-apoptotic controlling factor, and inhibition of NF-κB activation makes cells more sensitive to environmental stress and cytotoxic agents.

**[0008]** The proteasome inhibitor VELCADE® (bortezomib; N-2-pyrazinecarbonyl-L-phenylalanine-L-leucine-boronic acid) is the first proteasome inhibitor to achieve regulatory approval. Mitsiades et al., *Current Drug Targets,* 7:1341 (2006), reviews the clinical studies leading to the approval of bortezomib for the treatment of multiple myeloma patients who have received at least one prior therapy. Fisher et al., *J. Clin. Oncol.,* 30:4867, describes an international multi-center Phase II study confirming the activity of bortezomib in patients with relapsed or refractory mantle cell lymphoma. Ishii et al., *Anti-Cancer Agents in Medicinal Chemistry,* 7:359 (2007), and Roccaro et al., *Curr. Pharm. Biotech.,* 7:1341 (2006), discuss a number of molecular mechanisms that may contribute to the antitumor activities of bortezomib.

**[0009]** As evidenced by the above references, the proteasome represents an important target for therapeutic intervention. There is thus a continuing need for new and/or improved proteasome inhibitors.

## DESCRIPTION OF THE INVENTION

**[0010]** The present invention provides compounds that are effective inhibitors of the proteasome. These compounds are